

Pregnancy outcomes after fetal reduction and selective termination: A retrospective study

Outcomes fetal reduction and selective termination

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Abstract

Aim: Fetal reduction (FR) and selective termination (ST) are the procedures applied for multiple pregnancies that positively change the gestational outcomes. Results regarding the reliability of these procedures are variable. In this study, pregnancy outcomes of FR and ST procedures and pregnancy loss rates related to the procedure were evaluated.

Material and Methods: A total of 228 women with multifetal pregnancies, who underwent FR and ST in the Department of Gynecology and Obstetrics of Necmettin Erbakan University, Meram Faculty of Medicine between January 2007 and June 2017, were analyzed.

Result: The mean gestational week in those with FR was 11.7 (± 1.3). The mean gestational week in those with ST was 14.0 (± 3.1). The gestational week for ST was significantly higher than the gestational week for FR ($p < 0.001$). Out of a total of 132 pregnancies undergoing FR, there was a total pregnancy loss in one case (0.75%). There was no pregnancy loss in any of the pregnancies undergoing ST.

Discussion: With the increase in the number of fetuses, negative perinatal conditions such as preeclampsia, gestational diabetes, intrauterine growth retardation, postpartum hemorrhage and staying in the neonatal intensive care unit increase. In our study, it was observed that these risks were similar to the frequency in the general population in patients who underwent fetal reduction and selective termination.

The FR and ST procedures are successful methods to reduce fetal mortality and morbidity in the reduced numbers of fetuses, in conformity with ongoing pregnancies.

Keywords

Fetocid; Multifetal pregnancy; Pregnancy reduction; Selective termination

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Introduction

In line with the recent increase in the use of assisted reproductive techniques, the incidence of multifetal pregnancies has increased [1]. There has been an increase in the twin pregnancy rate by 2.8% to 3.4% [2]. Upon the increase in the multifetal pregnancy rates, the incidence of complications, such as prematurity, congenital anomalies, fetal growth restriction, twin-to-twin transfusion syndrome and fetal death, has also increased [3]. In order to reduce these complications, it was first attempted to reduce the number of embryos transferred in the assisted reproductive therapies [4].

Fetal Reduction (FR) is used to decrease fetal complications in the antenatal period. FR and selective termination (ST) aim to reduce the incidence of adverse perinatal outcomes in multifetal pregnancy by reducing the number of fetuses. While FR is implemented between the 10th and 13th weeks of the gestation, ST can be performed in any week of gestation when a fetal anomaly is detected [5].

The conventional techniques used for FR and ST are only suitable for multichorionic pregnancies; mono-chorionic pregnancies require special techniques and have higher pregnancy loss rates [5].

ST is known to yield better obstetric results when used prior to the 15th week [6]. At the same time, FR is known to increase the miscarriage rates in multifetal pregnancies while reducing the preterm delivery rates [7]. The primary aim of the FR and ST procedures is to increase the number of healthy fetuses to be taken home.

In this study, the complications of the FR and ST procedures performed in multifetal pregnancies and the outcomes of ongoing pregnancies were evaluated.

Material and Methods

This study was a retrospective study performed in the Department of Gynecology and Obstetrics of Necmettin Erbakan University, Meram Faculty of Medicine between January 2007 and June 2017, were analyzed. This study is in compliance with the principles of the Helsinki Declaration, and the approval was obtained from the Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine (2017/1012). A total of 228 women with multifetal pregnancies, who underwent FR and ST were included in this study. Seventy-two of these pregnant women who underwent FR and ST procedures were excluded for various reasons (delivery at a different center, the patients being inaccessible through file records, lack of data to be included in the study for accessible patients, unwillingness of the patients to take part in the study). The study included the remaining 156 patients. One hundred thirty-two of these patients underwent FR, while 24 underwent ST (Figure 1). The demographic data of the patients were retrospectively screened and included in the study form.

Informed consent was taken from the pregnant women scheduled to undergo FR and ST and from their spouses prior to the procedures. For the procedure, a GE Voluson 730 Pro ultrasound device was used. The procedure was always performed by the same operator (AA). The pregnant woman was placed in the supine position, and the abdomen was sterilized with an antiseptic solution (10% of polyvidone-iodine, Batticon®). The

sac was selected that has the thickest nuchal translucency (NT) regardless of the fetal gender, and is the most accessible one with the use of a needle, and is located away from the cervix and is located closest to the uterine fundus [8]. Then, using a 22G spinal needle, 1% of potassium chloride was injected intracardially into the fetus to be transabdominally reduced. Fetal cardiac activity is checked following each injection of 1 cc (0.01 mEq/mL). Until the fetal cardiac activity ceases, one cc of KCl solution is administered. The procedure was terminated following the development of asystole. The fetus to be chosen in ST is the fetus with a fetal anomaly.

The weeks of gestation of all pregnant women undergoing FR and ST, as well as the fetal weight at the delivery, Apgar scores, neonatal intensive care requirements, early and late neonatal complications were analyzed. Moreover, the patients who underwent FR and ST procedures were asked a single question whether they regretted having done the procedure, and their answers were recorded in the form of "yes" or "no". The two groups were compared in terms of the status of regret.

Statistical analysis

The SPSS 18.0 software package was used for the statistical analysis of the data. The Kolmogorov-Smirnov test was used to determine whether the numerical measures met the normal distribution assumption. Categorical measures were shown as numbers and percentages, the data distributed homogeneously as mean \pm standard deviation, and the data with non-homogeneous distribution as (median [minimum- maximum]). The Chi-Square test was used to compare the categorical measures between the groups. The independent t-test was used to analyze the homogeneously distributed data in the comparison of the numerical measures between the groups. The Kruskal-Wallis test was used to generally compare the non-normally distributed numerical measures between more than two groups. The statistical significance value was given as "p value" in all tests. A p-value of <0.05 was considered statistically significant.

Results

The mean maternal age at the time of delivery was 27.9 (± 4.3) in all pregnancies with FR. There were no significant differences between age, pre-gestation weight, gravida and parity in the comparison of the FR and ST patients (Table 1). Among multifetal pregnancy patients who underwent FR, 58/132 (44%) were the post-IVF ones, while this rate was 4/24 (16%) for the ST patients, and the cesarean section rate was significantly high in both groups ($p < 0.05$) (Table 1). The mean gestational week in those with FR was 11.7 (± 1.3). The mean gestational week in those with ST was 14.0 (± 3.1). The gestational week for ST was significantly higher than the gestational week for FR ($p < 0.001$).

Out of 132 patients undergoing FR, 20 were reduced to triplet pregnancy, 96 to twin pregnancies, and 16 to singleton pregnancies. Out of 24 patients undergoing ST, 23 were reduced to singleton pregnancy and 1 to twin pregnancy. One hundred seventeen (88.6%) of the patients undergoing FR had multi-chorionic/multi-amniotic multifetal pregnancies, while 15 pregnant women (11.4%) had dichorionic-triamniotic multifetal pregnancies. Fetuses with monochorionic placentation were

selected for the reduction of the dichorionic-triamniotic triplet pregnancies, and triplet pregnancies were reduced to singleton pregnancy in this manner.

Among the pregnant women undergoing FR, 12/132 (9%) got pregnant spontaneously, 58/132 (44%) through assisted reproductive techniques, 32/132 (24%) through intrauterine insemination following the ovulation induction, and 30/132 (23%) through planned coitus following the ovulation induction. As a group, ovulation induction was the most common way to get pregnant in the pregnant women undergoing FR, (62/132, 47%). Among the pregnant women undergoing ST, 10/24 (42%) got pregnant spontaneously, 4/24 (16%) through assisted reproductive techniques, 10/24 (42%) through intrauterine insemination following the ovulation indication.

Among the pregnancies undergoing FR, 4 (3%) were reduced from septuplet pregnancy, 4 (3%) from sextuplet pregnancy, 2 (1.5%) from quintuplet pregnancy, 32 (24%) from quadruplet pregnancy, and 54 (41%) from triplet pregnancy to twin pregnancy. Among the pregnancies reduced to triplet pregnancy, 10 (7.5%) were reduced from quadruplet pregnancy, 8 (6%) from quintuplet pregnancy, and 2 (1.5%) from septuplet pregnancy. The procedures were carried out in 2 different sessions at 7-day intervals in the pregnancies reduced from septuplet pregnancy to triplet and twin pregnancies. Fifteen (11.5%) of the pregnancies reduced to singleton pregnancy through FR were reduced from triplet pregnancy and 1 (1%) from twin pregnancy.

Only one (1/24, 4%) of the pregnancies undergoing ST was reduced from triplet pregnancy to twin pregnancy, while the remaining 23 (96%) were completely reduced from twin pregnancy to singleton pregnancy.

The pregnancies with FR were mostly reduced to twin pregnancy (96/132, 72.5%). The most frequent FR method used was the reduction from triplet pregnancy to twin pregnancy with 54 cases (41%).

The most common anomaly observed during ST was cystic hygroma (10/24, 41.6%). The total number of embryos reduced was 24 in a total of 24 cases undergoing ST.

Out of a total of 132 pregnancies undergoing FR, there was a total pregnancy loss in one case (0.75%). There was no pregnancy loss in any of the pregnancies undergoing ST.

When the patients undergoing FR were separately analyzed, it was found that the mean gestational week was 30.8 ± 3.7 weeks in the pregnant women reduced to triplet pregnancy, 35.4 ± 2.5 weeks in those reduced to a twin pregnancy, and 38.0 ± 0.8 weeks in those reduced to a singleton pregnancy. Except for one case, all pregnant women with ST were reduced from twin pregnancy to singleton pregnancy. The mean gestational week of 23 pregnant women reduced to singleton pregnancy was 37.8 ± 2.2 weeks. There was only one pregnant woman who was reduced to twin pregnancy. This pregnant woman delivered due to an early membrane rupture at 28 weeks of gestation. Furthermore, the pregnant women, who were reduced to triplet, twin and singleton pregnancies, were divided into three groups and compared among themselves. Accordingly, gestational week at the delivery, extremely early preterm deliveries (<32 weeks), preterm deliveries (37 weeks), infants with quite low weight of birth (1500 gr), infants with low weight of birth (2500

gr), 5th minute Apgar score lower than 7, GDM, preeclampsia, admission to NBIC unit, and perinatal mortality rates were significantly different (Table 2).

The results of the FR and ST cases reduced to singleton pregnancy are collectively summarized in Table 3. When the pregnancies that underwent FR-ST and reduced to a singleton pregnancy were compared, there were no significant differences between the two groups in terms of the gestational week, delivery before 37 weeks and before 32 weeks, birth weights lower than 2500 gr and 1500 gr, infants with a 5-minute APGAR score lower than 7, gestational diabetes, and preeclampsia (Table 3). Neither group had any infants lost in the neonatal period. Upon the comparison of both groups, it was seen that the pregnant women who underwent FR, 27/132 (20.4%) regretted it more compared to those who underwent ST, 1/24 (4.1%) and that this difference was statistically significant (p<0.05).

Table 1. Demographic data and clinical characteristics of pregnant women who underwent fetal reduction and selective termination

	FR ^a (±SD)	ST ^b (±SD)	p value
Maternal age * (year)	27,9 (±4,3)	28,0 (±6,1)	0,953
Gravida*	1,6 (±0,95)	1,8 (±0,9)	0,316
Parity*	0,2 (±0,5)	0,6 (±1,0)	0,071
Maternal weight * (kg)	68,4 (±4,2)	71,2 (±5,4)	0,884
Type of pregnancy**			<0,05
Spontaneous	12 (%9)	10 (%42)	
Assisted reproductive techniques	120 (%91)	14 (%58)	
Delivery**			<0,05
Vaginal delivery	23 (%17,6)	8 (%34)	
Cesarean section	108 (%82,4)	16 (%66)	
Processing week**	11,7 (±1,3)	14,0 (±3,1)	<0,001

^aFR: Fetal reduction
^bST: Selective termination
 *Data are presented as Mean ± SD (Student t test)
 **Data are presented as n (%) (Chi-square test)

Table 2. Obstetric outcomes of pregnancies with fetal reduction

	Reduced to triplet pregnancy (%) n=20	Reduced to twin pregnancy (%) n=95	Reduced to singleton pregnancy (%) n=16	p value
Gestational age at the time of delivery* (week)	30,8 ± 3,7	35,4 ± 2,5	38,0 ± 0,8	<0,05
Very early preterm deliveries** (<32 weeks)	9 (45)	15 (15,7)	1 (6,2)	<0,05
Preterm deliveries** (<37 weeks)	20 (100)	59 (62,1)	2 (12,4)	<0,05
Very low birth weight** (<1500 gr)	10 (50)	12 (12,6)	1 (6,2)	<0,05
Low birth weight** (<2500 gr)	20 (100)	44 (46,3)	4 (25)	<0,05
5th minute Apgar score lower than 7**	3 (15)	9 (9,4)	1 (6,25)	<0,05
Gestational Diabetes Mellitus **	5 (25)	14 (14,7)	2 (12,5)	<0,05
Preeclampsia**	2 (10)	8 (8,4)	1 (6,3)	<0,05
Admission to NICU ^b **	18 (90)	22 (23,1)	2 (12,5)	<0,05
Perinatal mortality**	2 (10)	4 (4,2)	0 (0)	<0,05

^aFR: Fetal reduction
^bNICU: Newborn intensive care unit
 *Data are presented as Mean ± SD (Student t test)
 **Data are presented as n (%) (Chi-square test)

Table 3. Comparison of the results of fetal reduction and selective termination pregnancies reduced to a single pregnancy

	Reduced to singleton pregnancy of FR ^a (%) n=16	Reduced to singleton pregnancy of ST ^b (%) n=23	p value
Gestational age at delivery* (week)	38,0 ± 0,8	37,8 ± 2,2	0,255
Very early preterm delivery** (<32 weeks)	1 (6,2)	1 (4,3)	0,273
Preterm delivery** (<37 weeks)	2 (12,4)	3 (12,9)	0,521
Very low birth weight** (<1500 gr)	1 (6,2)	1 (4,3)	0,294
Low birth weight** (<2500 gr)	4 (25)	4 (17,3)	0,282
5th minute Apgar score lower than 7**	1 (6,25)	1 (4,3)	0,451
Gestational Diabetes Mellitus**	2 (12,5)	2 (8,6)	0,214
Preeclampsia**	1 (6,3)	1 (4,3)	0,233
Admission to NICU**	2 (12,5)	1 (4,3)	0,092
Perinatal mortality**	-	-	-

aFR: Fetal reduction
 bST: Selective termination
 cNICU: Newborn intensive care unit
 *Data are presented as Mean ± SD (Student t test)
 **Data are presented as n (%) (Chi-square test)

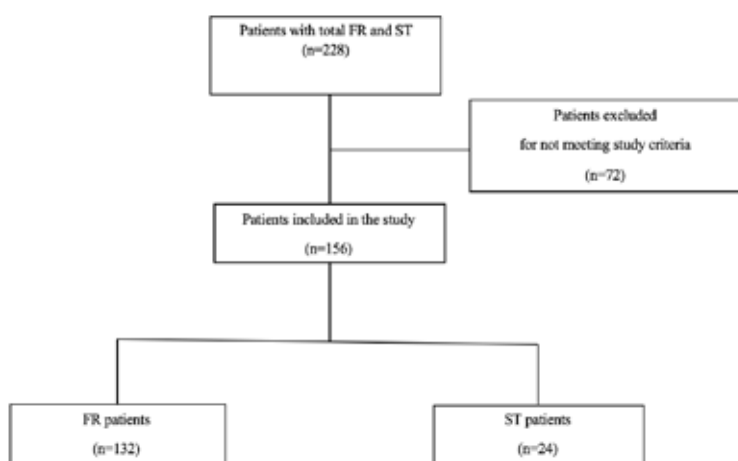


Figure 1. Study flowchart
 FR; Fetal reduction, ST; Selective termination

Discussion

The number of multifetal pregnancies has risen significantly as a consequence of the increase in advanced age pregnancies and the assisted reproductive techniques becoming widespread in recent years. The distinct increase in the incidence of multifetal pregnancies brings along negative perinatal outcomes [9]. Premature delivery, intrauterine growth restrictions, structural and chromosomal anomalies are the major causes of adverse perinatal results [10]. Perinatal results are getting dramatically worse particularly in multifetal pregnancies with 3 or more fetuses [11]. This situation, as a consequence, led to the idea of reducing such pregnancies to a lower number of multifetal pregnancies, which has been implemented since then. In our study, 2/20 (10%) of the fetuses delivered through pregnancies treated with FR and reduced to triplet pregnancy were lost in the perinatal period, while 4/95 (4.2%) of those reduced to twin pregnancy were lost in the perinatal period.

These data demonstrate similar features with the multifetal pregnancies that occurred spontaneously and in the same numbers [12]. No loss was observed neither in the post-procedural period nor in the perinatal period in the FR and ST pregnancies that were reduced to a singleton pregnancy.

There are quite varying numbers in the literature with regard to the methods of delivery of patients who underwent FR and ST [13, 14]. Among those undergoing FR in this study, 82.4% had cesarean section delivery, while 17.6% had a vaginal delivery. The high cesarean section rate is associated with the pregnancies being treatment-induced gestations, and therefore with social indications.

Multifetal pregnancy also increases the risk of gestational complications of the mother, including preeclampsia, postpartum hemorrhage and gestational diabetes [15]. This is directly associated with the rise in the number of fetuses of multifetal pregnancies. Upon the analysis of the pregnancies that were reduced to single fetuses through FR and ST in our study, it was seen that the prevalence of preeclampsia and GDM was at rates that were similar to the prevalence of the same in the general population (respectively 6.3% and 4.3% for preeclampsia; respectively 12.5% and 8.6% for GMD in the order of prevalence for FR and ST).

Despite being controversial, there are some opinions suggesting that FR can also be considered for twin pregnancies in the absence of medical or obstetric indications (e.g. Maternal heart disease, history of a preterm single delivery, cervical failure resulting in pregnancy loss) [16,17]. In this study, only one patient was reduced from twin pregnancy to singleton pregnancy through FR. This procedure was implemented due to maternal heart disease (history of heart transplantation).

The involuntary pregnancy loss was reported to be 5.4% in a monocenter series in which 1000 FR patients were analyzed [18]. The rate of loss was reported as 2.5% in those reduced from twin pregnancy to singleton pregnancy, and as 5% in those reduced from triplet pregnancy to singleton pregnancy. The pregnancy loss prior to week 24 in the post-ST period was reported as 4% in a single-center series consisting of 200 patients [19]. In a multicenter series, 402 cases were analyzed and this rate was found to be 7.5% [20]. Any complete pregnancy loss within 10 days in the post-procedure period is considered a procedure-induced pregnancy loss. Accordingly, out of 132 pregnancies in total that underwent FR in our series, one had a total pregnancy loss (0.75%). This was a pregnant woman who was reduced from septuplet pregnancy to twin pregnancy. No pregnancy loss occurred in any of the pregnancies that underwent ST. The fact that the rate of pregnancy loss in our study was much lower than the literature data can be explained by the fact that the procedures were conducted by the same operator at all times throughout the study. Much of the literature data consist of a review of the data from procedures conducted by multiple operators. Post-FR pregnancy results, including the rates of total pregnancy loss and prematurity, improve with increasing operator experience [18].

The multifetal pregnancies reduced to singleton pregnancy result in fewer preterm deliveries compared to the multifetal pregnancies reduced to twin pregnancy [21]. In our study, deliveries prior to week 37 in pregnancies with FR were

observed in all pregnancies that were reduced to triplet pregnancy, in 62.1% of the pregnancies that were reduced to a twin pregnancy, and in 12.4% of the pregnancies that were reduced to a singleton pregnancy. Similarly, deliveries prior to 32 weeks in pregnancies with FR were observed in 45% of the pregnancies reduced to triplet pregnancy, in 15.7% of the pregnancies reduced to a twin pregnancy, and in 6.2% of the pregnancies reduced to a singleton pregnancy. These preterm delivery rates are similar to those in multifetal pregnancies and support the fact that the FR procedure does not constitute any additional risks for preterm delivery.

Alvarado et al. reported that the rate of pregnancy loss was 3.6% in 28 dichorionic pregnancies undergoing ST, and that the rate of delivery prior to week 34 was reduced by 11.8% [22]. Furthermore, in the literature, it is recommended that the ST procedure be performed in the advanced weeks rather than early. [23]. In our study, the preterm delivery prevalence in the FT patient group under 32 weeks was 45% in those reduced to triplet pregnancy, 15.2% in those reduced to a twin pregnancy, and 6.2% in those reduced to a singleton pregnancy. In the ST patient group, however, the prevalence of preterm delivery under 32 weeks was 4.3% in the patients that were reduced to a singleton pregnancy. These data are in concordance with the rates of preterm delivery reported in the literature.

Studies evaluating birth weights in pregnancies with FR and ST support the fact that birth weights in these pregnancies do not differ from spontaneous multifetal pregnancies in the same numbers [24]. When the FR and ST cases reduced to singleton pregnancies were compared, no significant differences could be observed in terms of birth weights under 2500 g and under 1500 g.

A large number of studies showed that the pregnancies with FR and ST, the Apgar score at the time of delivery and the requirement for admission to the NBIC unit were not different from the spontaneous multifetal pregnancies in the same numbers. Tse et al. analyzed the results of 52 triplet pregnancies and showed that the weight of birth increased in pregnant women with FR and that the newborn intensive care requirement reduced, while the preterm delivery rate reduced [25]. Among the fetuses delivered through pregnancies reduced from triplet pregnancy after FR and ST in our study, 90% were admitted to the NBIC unit, as well as 23% of the fetuses delivered through pregnancies reduced to a twin pregnancy, and 6.3% of the fetuses delivered through pregnancies reduced to a singleton pregnancy. Among the fetuses delivered through pregnancies reduced to singleton pregnancy after ST, 4.3% were admitted to the NBIC unit. Upon the comparison of the FR and ST cases reduced to a singleton pregnancy, no differences could be observed with regard to the prevalence of fetuses admitted to the NBIC unit ($p=0.75$). Out of 23 fetuses in total that were delivered through pregnancies reduced to singleton pregnancy after ST, one (4.3%) was admitted to the NBIC unit. No neonatal deaths occurred among these infants. These data are in concordance with the literature.

No studies were seen in the literature on what families that went through FR and ST felt about this decision they made. In our study, the patients were asked whether they regretted the procedure they went through. Among the mothers that

underwent FR, 20.4% answered "I regret it", in addition to 4.1% of the mothers who underwent ST and gave the same answer. Upon the comparison of both groups, it was seen that the pregnant women who underwent FR regretted it more compared to those who underwent ST, and that this difference was statistically significant ($p<0.05$). This was probably caused by the termination of a fetus with fetal anomalies, which was the reason to have ST. On the contrary, the fact that a normal fetus is "seemingly" terminated in FR pregnancies explains why this rate is significantly high.

Conclusion

The FR and ST procedures are successful methods to reduce fetal mortality and morbidity in the reduced numbers of fetuses consistent with ongoing pregnancies.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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